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(54) Acylanilides, process for their manufacture, their use in pharmaceutical and veterinary compositions and a method of producing an antiandrogenic effect in a warm-blooded animal.

(57) The disclosure relates to novel 3,4-disubstituted-branched-chain-acylanilides, processes for their manufacture and pharmaceutical compositions containing them. The compounds possess anti-androgenic activity. Representative of the compounds disclosed is 3,4-dicyano-isobutyranilide.

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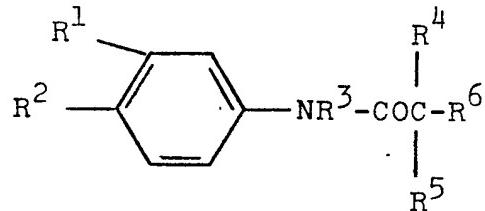
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AMIDES

This invention relates to new amides and more particularly it relates to novel acylanilides which possess anti-androgenic properties.

According to the invention there is provided an acylanilide of the formula:-



wherein at least one of R^1 and R^2 is cyano and wherein the other of R^1 and R^2 is cyano, nitro, trifluoromethyl, chloro, bromo or iodo, or has the formula $-\text{CONR}^{11}\text{R}^{12}$, wherein R^{11} and R^{12} , which may be the same or different, each is hydrogen or alkyl of up to 4 carbon atoms; wherein R^3 is hydrogen or alkyl of up to 4 carbon atoms; wherein either R^4 and R^5 , which may be the same or different, each is alkyl of up to 4 carbon atoms, or R^4 and R^5 are joined together with the adjacent carbon atom to form cycloalkyl of 3 or 4 carbon atoms; and wherein R^6 is hydrogen, hydroxy, halogen, alkyl, hydroxy-alkyl or alkoxy each of up to 4 carbon atoms, or acyloxy of up to 15 carbon atoms; provided that when R^2 is cyano, R^3 and R^6 are both hydrogen and

R⁴ and R⁵ are both methyl, R¹ is not chloro.

A suitable value for R¹, R² or R⁶ when it is halogen is fluoro, chloro, bromo or iodo.

5 A suitable value for R³, R⁴, R⁵, R⁶, R¹¹ or R¹² when it is alkyl is, for example, methyl or ethyl.

A suitable value for R⁶ when it is hydroxy-alkyl or alkoxy is, for example, hydroxymethyl, methoxy or ethoxy.

10 A suitable value for R⁶ when it is acyloxy is is, for example, alkanoyloxy of up to 15 carbon atoms, for example acetoxy, propionyloxy, decanoyloxy or codecanoyloxy.

15 It will be observed that the acylanilide derivative of the invention may possess an asymmetric carbon atom, namely the carbon atom of the -CR⁴R⁵R⁶ group when R⁴, R⁵ and R⁶ are all different, and it may then exist in racemic and optically-active forms. It is to be understood that this invention encompasses the racemic form of such an acylanilide derivative and any optically-active 20 form which possesses anti-androgenic activity, it being a matter of common general knowledge how a racemic compound may be resolved into its optically-active forms and how any anti-androgenic activity present in any of these forms may be determined.

25 One preferred acylanilide of the invention has the formula stated above wherein R¹ is cyano, R² is cyano, chloro, bromo, iodo or nitro, R³ is hydrogen or alkyl of up to 4 carbon atoms, either R⁴ is methyl or ethyl and R⁵ is methyl or ethyl, or R⁴ and R⁵ together with the adjacent carbon atom form cyclopropyl, and R⁶ is hydrogen, hydroxy, 30 chloro, bromo, methyl, hydroxymethyl or methoxy, or alkanoyloxy of up to 12 carbon atoms.

35 A second preferred acylanilide of the invention has the formula stated above wherein R¹ is nitro or trifluoromethyl, R² is cyano and R³, R⁴, R⁵ and R⁶ have the meanings stated in the last paragraph above.

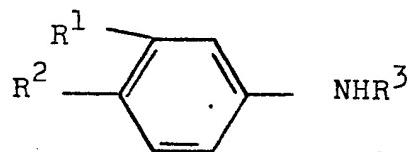
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Specific acylanilides of the invention are hereinafter described in the Examples.

Particularly active compounds are 3,4-dicyanoisobutyrylanilide, 3,4-dicyano-(2-hydroxy-2-methylpropionyl)anilide, 3,4-dicyano-N-methylisobutyrylanilide, 3,4-dicyano-(2-methoxy-2-methylpropionyl)anilide and 4-cyano-3-trifluoromethyl-(2-hydroxy-2-methylpropionyl)anilide, and of these the last two are preferred.

10 The acylanilides of the invention may be manufactured by any chemical process known to be suitable for the manufacture of chemically-analogous compounds.

15 A preferred process for the manufacture of an acylanilide of the invention comprises the reaction of an amine of the formula



wherein R^1 , R^2 and R^3 have the meanings stated above, with an acid of the formula

20 $\text{HOOCR}^4\text{R}^5\text{R}^6$

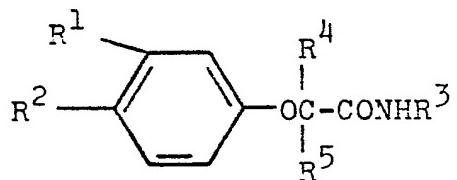
wherein R^4 , R^5 and R^6 have the meanings stated above, or with a reactive derivative of said acid.

25 A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester. The reactive derivative may be prepared in situ, for example by reacting the acid with thionyl chloride in a dipolar aprotic solvent such as N,N-dimethylacetamide, hexamethylphosphoric triamide or N-methylpyrrolidinone.

30 An alternative process for the manufacture of an acylanilide derivative of the invention

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wherein R⁶ is hydroxy comprises the Smiles' rearrangement of an amide of the formula:-



wherein R¹, R², R³, R⁴ and R⁵ have the meanings
5 stated above.

The rearrangement may be carried out by treating the amide with a strong base, for example an alkali metal hydride, for example sodium hydride, under anhydrous conditions. The reaction
10 is conveniently carried out at laboratory temperature.

An acylanilide of the invention wherein R³ is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R³ is hydrogen.

An acylanilide of the invention wherein R⁶ is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R⁶ is hydroxy, and an acylanilide of the invention wherein R⁶ is hydroxy may be prepared by the hydrolysis of the
20 corresponding acylanilide wherein R⁶ is acyloxy.

As stated above, an acylanilide of the invention possesses anti-androgenic properties as demonstrated by its ability to decrease the weight of the seminal vesicles and ventral prostate of a
25 castrated male rat when administered concurrently with testosterone propionate. An acylanilide of the invention may therefore be used in the treatment of, for example, malignant or benign prostatic disease or of androgen-dependent disease conditions,
30 such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

The acylanilide of the invention may be administered to a warm-blooded animal in the form of a pharmaceutical or veterinary composition which comprises the acylanilide in association with a pharmaceutically-acceptable diluent or carrier.

5 The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution
10 or suspension suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration, or be in the form of a suppository.

15 The composition may additionally contain one or more drugs selected from antioestrogens, for example tamoxifen; progestins, for example medroxy-progesterone acetate; inhibitors of gonadotrophin secretion, for example danazol; cytotoxic agents, for example cyclophosphamide; antibiotics, for
20 example penicillin or oxytetracyclin; and anti-inflammatory agents, for example, especially for topical use, fluocinolone acetonide.

25 The acylanilide of the invention will normally be administered to a warm blooded animal at a dose of between 0.1 mg. and 25 mg. per kg. bodyweight.

The invention is illustrated but not limited by the following Examples:-

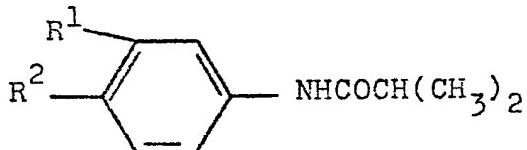
Example 1

30 Isobutyryl chloride (3 ml.) is added to a stirred solution of 3,4-dicyanoaniline (0.7 g.) in pyridine (15 ml.) and the mixture is stirred at laboratory temperature for 3 hours and then diluted with water (150 ml.). The mixture is extracted
35 with ethyl acetate and the extract is washed with water, dried over magnesium sulphate and evaporated

to dryness. The residue is crystallised from a mixture of toluene and petroleum ether (b.p. 60-80°C.) and there is thus obtained 3,4-dicyano-isobutyrylanilide, m.p. 119-121°C.

5 The process described above is repeated except that the appropriate aniline is used in place of 3,4-dicyanoaniline. There are thus similarly obtained the compounds shown in the following table:-

10



R ¹	R ²	m.p. (°C.)
cyano	bromo	146-148
nitro	cyano	133-135
cyano	chloro	139-141

15

The process described in the first paragraph above is repeated except that 2-acetoxy-2-methylpropionyl chloride is used in place of isobutyryl chloride. There is thus obtained 3,4-dicyano-(2-acetoxy-2-methylpropionyl)anilide, m.p. 154-156°C.

Example 2

A mixture of 3,4-dicyanoaniline (2 g.) and 2-hydroxy-2-methylpropionic acid (6 g.) is heated at 20 160°C. for 4 hours and then cooled and shaken with a mixture of ethyl acetate and water. The ethyl acetate layer is separated, washed with dilute aqueous sodium hydroxide solution and then with

water, dried over magnesium sulphate and evaporated to dryness. The residue is chromatographed on a silica gel column (200 g.) using a 15% v/v solution of ethyl acetate in chloroform as eluant. The
5 eluate is collected and evaporated to dryness and the residue is crystallised from ethyl acetate. There is thus obtained 3,4-dicyano-(2-hydroxy-2-methylpropionyl)anilide, m.p. 198-200 °C.

Example 3

10 Sodium hydride (100 mg. of a 60% dispersion in mineral oil from which the oil has been removed by washing with petroleum ether b.p. 60-80 °C.) is added to a stirred solution of 2-(3,4-dicyanophenoxy)-2-methylpropionamide (0.5 g.) in N,N-dimethylformamide (10 ml.) which is maintained at 20 °C., and the mixture is stirred at this temperature for 30 minutes. Water (100 ml.) is added, the mixture is extracted with ethyl acetate and the extract is washed with water, dried over magnesium
15 sulphate and evaporated to dryness. The residue is crystallised from toluene and there is thus obtained 3,4-dicyano-(2-hydroxy-2-methylpropionyl)anilide, m.p. 198-200 °C.

20 The 2-(3,4-dicyanophenoxy)-2-methylpropionamide used as starting material may be obtained as follows:-

25 Sodium hydroxide (2.25 g.) is added to a solution of 3,4-dicyanophenol (2.0 g.) in acetone (100 ml.), the mixture is heated to 50 °C. and a
30 solution of chloroform (1.4 ml.) in acetone (10 ml.) is added dropwise. The mixture is heated under reflux for 5 hours and the acetone is then removed by evaporation. The residue is shaken with diethyl ether and water and the aqueous layer is separated,
35 acidified with aqueous hydrochloric acid and extracted with ethyl acetate. The extract is

washed with water, dried over magnesium sulphate and evaporated to dryness. Thionyl chloride (30 ml.) is added to the residue (which consists of 2-(3,4-dicyanophenoxy)-2-methylpropionic acid) and
5 the mixture is heated under reflux for 15 minutes and then evaporated to dryness. The residue is dissolved in dioxan (100 ml.), concentrated aqueous ammonium hydroxide solution (50 ml.) is added and the mixture is stirred at 20°C. for 30 minutes.
10 Water (500 ml.) is added, the mixture is extracted with ethyl acetate and the extract is washed with water, dried over magnesium sulphate and evaporated to dryness. The residue is crystallised from toluene and there is thus obtained 2-(3,4-dicyano-
15 phenoxy)-2-methylpropionamide, m.p. 141-143°C.

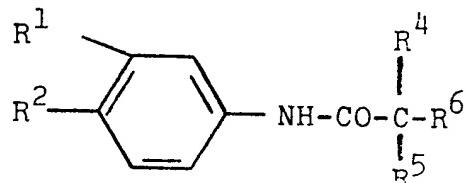
Example 4

Thionyl chloride (1.5 ml.) is added to a stirred solution of 2-hydroxy-2-methylpropionic acid (2.0 g.) in hexamethylphosphoric triamide (4 ml.)
20 which is cooled to -10°C., and the mixture is stirred at -10°C. for 1 hour. 3,4-Dicyanoaniline (0.3 g.) is added, and the mixture is stirred for 4 hours at laboratory temperature and then diluted with water. The mixture is extracted with ethyl acetate and the extract is washed with water, dried over magnesium sulphate and evaporated to dryness. The residue is dissolved in ethyl acetate and the solution is passed through a short column of silica gel. The eluate is evaporated to dryness and the
25 residue is crystallised from toluene. There is thus obtained 3,4-dicyano-(2-hydroxy-2-methylpropionyl)-anilide, m.p. 198-200°C.

Example 5

The process described in Example 4 is repeated using the appropriate acid and the appropriate aniline derivative as starting materials.

There are thus obtained the anilides described in the following table:-



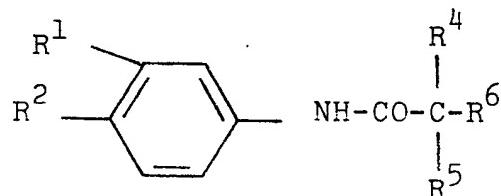
R¹	R²	R⁴	R⁵	h	m.p. (°C.)
ciano	ciano	methyl	methyl	methoxy	178-180
ciano	ciano	methyl	methyl	hydroxymethyl	162-164
ciano	ciano	methyl	methyl	bromo	147-150
ciano	ciano	methyl	ethyl	hydroxy	142-144
ciano	ciano	ethyl	ethyl	hydroxy	132-135
ciano	iodo	methyl	methyl	hydroxy	176-182
trifluoro-methyl	ciano	methyl	methyl	hydroxy	139-140

Example 6

5

The process described in Example 1 is repeated except that the appropriate acyl chloride and the appropriate aniline are used as starting materials. There are thus obtained the anilides described in the following table:-

10



R ¹	R ²	R ⁴	R ⁵	R ⁶	m.p.(°C.)
cyano	cyano	methyl	methyl	chloro	171-174
cyano	cyano	methyl	methyl	methyl	185-187
trifluoro-methyl	cyano	methyl	methyl	H	134-136

Example 7

Thionyl chloride (0.72 g.) is added dropwise to a stirred solution of cyclopropane-carboxylic acid (0.516 g.) in N,N-dimethylacetamide (15 ml.) which is maintained at -20°C., and the mixture is stirred at that temperature for 1 hour. 3,4-Dicyanoaniline (0.572 g.) is added and the mixture is stirred at laboratory temperature for 16 hours and then diluted with water (50 ml.). The mixture is extracted with ethyl acetate and the extract is washed with water, dried and evaporated to dryness. The residue is crystallised once from toluene and twice from ethyl acetate, and there is thus obtained 3,4-dicyano-(cycloprop-anecarbonyl)anilide, m.p. 176-178°C.

The process described above is repeated except that 2-hydroxy-2-methylpropionic acid and 3-cyano-4-nitroaniline are used as starting materials, and that the crude reaction product is purified by chromatography on a silica gel column using a 1:4 v/v mixture of ethyl acetate and toluene as eluting solvent. The oily product thus obtained is triturated with petroleum ether (b.p. 60-80°C) and the solid product thus obtained is crystallised from toluene. There is thus obtained 3-cyano-4-nitro-(2-hydroxy-2-methylpropionyl)anilide, m.p. 148-152°C.

Example 8

3,4-Dicyanoisobutyranilide (0.67 g.) is added to a suspension of sodium hydride (0.11 g. of

a 60% dispersion in mineral oil from which the oil has been washed off with petroleum ether b.p. 40-60°C.) in N,N-dimethylformamide (20 ml.), and methyl iodide (4 ml.) is added after the effervescence has ceased. The mixture is kept at laboratory temperature for 16 hours, water (50 ml.) is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried and evaporated to dryness and the residue is crystallised from toluene.

10 There is thus obtained 3,4-dicyano-N-methylisobutyranilide, m.p. 122-123°C.

The process described above is repeated using ethyl iodide or n-butyliodide in place of methyl iodide. There are thus obtained, respectively,

15 3,4-dicyano-N-ethylisobutyranilide, m.p. 120-122°C. and N-butyl-3,4-dicyanoisobutyranilide, m.p. 143-145°C.

Example 9

A mixture of 3,4-dicyano-(2-hydroxy-2-methylpropionyl)anilide (0.2 g.), decanoyl chloride (1.5 ml.) and concentrated aqueous hydrochloric acid (0.1 ml.) is heated at 50°C. for 5 hours and then diluted with water. The mixture is extracted with ether and the extract is washed twice with

20 saturated sodium bicarbonate solution, once with water and once with saturated sodium chloride solution, dried and evaporated to dryness. The residue is chromatographed on a silica gel column (10 g.) using a 1:9 v/v mixture of ethyl acetate and toluene

25 as eluting solvent. The product obtained is crystallised from a mixture of ether and petroleum ether (b.p. 40-60°C.) and there is thus obtained 3,4-dicyano-(2-decanoyloxy-2-methylpropionyl)anilide, m.p. 135-137°C.

30

35 The process described above is repeated except that lauroyl chloride is used in place of

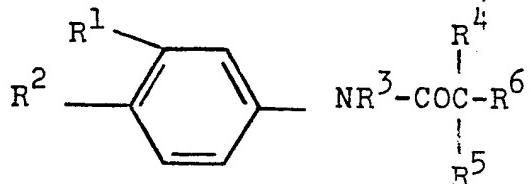
decanoyl chloride. There is thus obtained 3,4-dicyano-(2-dodecanoyloxy-2-methylpropionyl)anilide, m.p. 137-139°C.

Example 10

5 A solution of 3,4-dicyano-(2-acetoxy-2-methylpropionyl)anilide (0.0625 g.) in methanol (5 ml.) is added to a solution of sodium carbonate (0.008 g.) in water (0.5 ml.) and the mixture is stirred at laboratory temperature for 15 minutes
10 and then diluted with water. The mixture is extracted with ether and the extract is washed with water and then with saturated sodium chloride solution, dried and evaporated to dryness. The residue is crystallised from toluene and there is
15 thus obtained 3,4-dicyano-(2-hydroxy-2-methyl-propionyl)anilide, m.p. 198-200°C.

What we claim is:-

1. An acylanilide of the formula:-



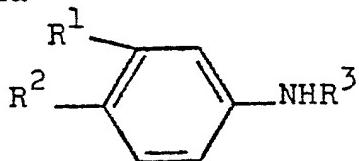
- wherein at least one of R¹ and R² is cyano and
5 wherein the other of R¹ and R² is cyano, nitro,
trifluoromethyl, chloro, bromo or iodo, or has the
formula $\text{CONR}^{11}\text{R}^{12}$, wherein R¹¹ and R¹², which may
be the same or different, each is hydrogen or alkyl
of up to 4 carbon atoms; wherein R³ is hydrogen or
10 alkyl of up to 4 carbon atoms; wherein either R⁴
and R⁵, which may be the same or different, each is
alkyl of up to 4 carbon atoms; or R⁴ and R⁵ are
joined together with the adjacent carbon atom to
form cycloalkyl of 3 or 4 carbon atoms; and wherein
15 R⁶ is hydrogen, hydroxy, halogen; alkyl, hydroxy-
alkyl or alkoxy each of up to 4 carbon atoms, or
acyloxy of up to 15 carbon atoms; provided that
when R² is cyano, R³ and R⁶ are both hydrogen and
R⁴ and R⁵ are both methyl, R¹ is not chloro.
- 20 2. An acylanilide as claimed in claim 1
wherein R¹ is cyano, R² is cyano, chloro, bromo,
iodo or nitro, R³ is hydrogen or alkyl of up to 4
carbon atoms, either R⁴ is methyl or ethyl and R⁵
is methyl or ethyl, or R⁴ and R⁵ together with the
25 adjacent carbon atom form cyclopropyl, and R⁶ is
hydrogen, hydroxy, chloro, bromo, methyl, hydroxy-
methyl or methoxy, or alkanoyloxy of up to 12
carbon atoms.
3. An acylanilide as claimed in claim 1
30 wherein R¹ is nitro or trifluoromethyl, R² is
cyano and R³, R⁴, R⁵ and R⁶ have the meanings
stated in claim 2.
4. The compound 3,4-dicyanoisobutyrylanilide or
3,4-dicyano-(2-hydroxy-2-methylpropionyl)anilide.

5. The compound 3,4-dicyano-N-methyl-isobutyrylanilide.

6. The compound 3,4-dicyano-(2-methoxy-2-methylpropionyl)anilide or 4-cyano-3-trifluoromethyl-(2-hydroxy-2-methylpropionyl)anilide.

5 7. A process for the manufacture of an acylanilide, claimed in any of claims 1 to 6, which comprises either the reaction of an amine of the formula

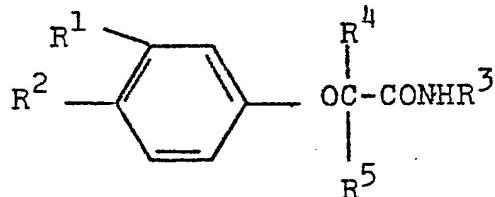
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wherein R¹, R² and R³ have the meanings stated in claim 1, 2 or 3, with an acid of the formula



15 wherein R⁴, R⁵ and R⁶ have the meanings stated in claim 1, 2 or 3, or with a reactive derivative of said acid; or, for the manufacture of an acylanilide wherein R⁶ is hydroxy, the Smiles' rearrangement of an amide of the formula:-



20 wherein R¹, R², R³, R⁴ and R⁵ have the meanings stated above;

whereafter an acylanilide wherein R³ is hydrogen may be alkylated to provide the corresponding acylanilide wherein R³ is alkyl of up to 25 4 carbon atoms; or

an acylanilide wherein R⁶ is hydroxy may be acylated to provide the corresponding acylanilide wherein R⁶ is acyloxy of up to 15 carbon atoms; or an acylanilide wherein R⁶ is acyloxy may

be hydrolysed to the corresponding acylanilide wherein R⁶ is hydroxy.

8. A pharmaceutical or veterinary composition which comprises an acylanilide, claimed in any of 5 claims 1 to 6, in association with a pharmaceutically-acceptable diluent or carrier.
9. A composition as claimed in claim 8 which additionally contains one or more drugs selected from antioestrogens, progestins, inhibitors of 10 gonadotrophin secretion, cytotoxic agents, antibiotics, and antiinflammatory agents.
10. A method of producing an antiandrogenic effect in a warm-blooded animal in need of such an effect which comprises administering to said 15 animal an effective amount of an acylanilide claimed in any of claims 1 to 6.

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DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p>Chemical Abstracts, vol. 81, no. 15, 14 October 1974, Columbus, Ohio, USA E.M. GRIVSKY et al "Syntheses of 2-chloro-4-acetylaminobenzonitrile isomers and structurally related compounds with biological activi- ties" page 433, column 2, abstract no. 91190y & Ind. Chim. Belge, vol. 39, no. 5; 1974 pages 490 to 500 --</p> <p>Chemical Abstracts, vol. 83, no. 17, 27 October 1975, Columbus, Ohio, USA R.O. NERI et al "Biological aspects of antiandrogens" page 61, column 1, abstract no. 142 143m & J. Steroid Biochem. vol. 6, no. 6; 1975, pages 815 to 819 -----</p>	1	<p>C 07 C 121/78 A 61 K 31/275// C 07 C 121/75</p>
		1,8	<p>TECHNICAL FIELDS SEARCHED (Int.Cl.)</p> <p>A 61 K 31/275 C 07 C 121/52 C 07 C 121/54 C 07 C 121/78</p>
			<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p>
	<input checked="" type="checkbox"/> The present search report has been drawn up for all claims		<p>& member of the same patent family. corresponding document</p>
Place of search	Date of completion of the search	Examiner	
Berlin	02-04-1979	STOOS	



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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<p>Chemical Abstracts, vol. 81, no. 15, 14 October 1974, Columbus, Ohio, USA E.M. GRIVSKY et al "Syntheses of 2-chloro-4-acetylaminobenzonitrile isomers and structurally related compounds with biological activi- ties" page 433, column 2, abstract no. 91190y & Ind. Chim. Belge, vol. 39, no. 5; 1974 pages 490 to 500 --</p> <p>Chemical Abstracts, vol. 83, no. 17, 27 October 1975, Columbus, Ohio, USA R.O. NERI et al "Biological aspects of antiandrogens" page 61, column 1, abstract no. 142 143m & J. Steroid Biochem. vol. 6, no. 6; 1975, pages 815 to 819 -----</p>		<p>C 07 C 121/78 A 61 K 31/275// C 07 C 121/75</p> <p>TECHNICAL FIELDS SEARCHED (Int.Cl.²)</p> <p>A 61 K 31/275 C 07 C 121/52 C 07 C 121/54 C 07 C 121/78</p>
		1,8	<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p> <p>&: member of the same patent family, corresponding document</p>
<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
Berlin	02-04-1979	STOOS	
EPO Form 1503.1 06.78			